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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,908	08/01/2005	Bernd Kuhn	Le A 36 031	7332

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

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07/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,908	KUHN ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008 and 29 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 29 Dec 2008, and Applicant's Amendment and Remarks, filed 29 Apr 2009.

Applicant's Amendment and Remarks filed 29 Apr 2009, stating that the translation of the certified copy of the priority document is accurate and perfecting the claim of foreign priority as requested by Examiner in the telephone interview on 29 Apr 2009, is entered.

This application is the national stage entry of PCT/EP03/03327, filed 31 Mar 2003; and claims benefit under 35 USC 119(a-d) of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002; currently an English language translation of this foreign priority document is of record and the claim of foreign priority has been perfected.

Claims 1-10 are pending in the current application.

Rejections Withdrawn

Applicant's Amendment, filed 29 Apr 2009, with respect to claims 1-3 rejected under 35 U.S.C. 102(a) as being anticipated by Mauler et al (J. Pharmacol. Exp. Ther., 2002, of record – Published online June 13, 2002. Mailed June 14, 2002) has been fully considered and is persuasive, as the claim of foreign priority to GERMANY 10215942.4,

filed 11 Apr 2002 has been perfected, therefore Mauler et al. does not qualify as a reference under 35 U.S.C. 102(a).

This rejection has been **withdrawn**.

Applicant's Amendment, filed 29 Apr 2009, with respect to claims 1-4, 8 and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Mauler et al (J. Pharmacol. Exp. Ther., 2002) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) has been fully considered and is persuasive, as the claim of foreign priority to GERMANY 10215942.4, filed 11 Apr 2002 has been perfected, therefore Mauler et al. does not qualify as a reference under 35 U.S.C. 102(a) and Szabo et al. alone does not teach all limitations of the claims.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 29 Apr 2009, with respect to claims 1- 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Mauler et al (J. Pharmacol. Exp. Ther., 2002) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000) has been fully considered and is persuasive, as the claim of foreign priority to GERMANY 10215942.4, filed 11 Apr 2002 has been perfected, therefore Mauler et al. does not qualify as a reference under 35 U.S.C. 102(a) and Szabo et al. and Nakazi et al alone do not teach all limitations of the claims.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 29 Apr 2009, with respect to claims 1-4 and 8-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Mauler et al (J. Pharmacol. Exp. Ther., 2002) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Yamada (US 5,807,337) has been fully considered and is persuasive, as the claim of foreign priority to GERMANY 10215942.4, filed 11 Apr 2002 has been perfected, therefore Mauler et al. does not qualify as a reference under 35 U.S.C. 102(a) and Szabo et al. and Yamada alone do not teach all limitations of the claims.

This rejection has been **withdrawn**.

The following grounds of rejection are reiterated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record).

Mittendorf discloses a pharmaceutical composition comprising the compound (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate (column 199, claim 1 and column 200, claim 5). Mittendorf discloses the compound is a cannabinoid receptor agonist (column 1, lines 23-50). This composition is suitable for administration as a continuous infusion (column 36, lines 55-58). Mittendorf discloses the composition wherein the solvent is aqueous NaCl (column 36, lines 15-20). Mittendorf discloses the compound with suitable excipients and envisions the use of organic solvents as auxiliary solvents if water is used as a diluent (column 37, lines 20-30). Mittendorf discloses the dosage of the compound of 0.01 to 10 mg/kg (column 37, lines 35-37).

Mittendorf does not specifically disclose the excipient cyclodextrin or the ratio of compound to cyclodextrin.

Szabo teaches that an aqueous solution diluted with a 19% cyclodextrin solution is a suitable vehicle for infusing the cannabinoid receptor agonists, WIN 55,212-2 and CP 55,940. See page 820, 2nd paragraph under "Drugs." The reference further teaches that other similar drugs are dissolved in ethanol and saline.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising said for infusion using any suitable physiologically solution for administration as taught by Mittendorf. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further within the scope of the artisan to modify this vehicle with other standard physiological solvents, such as ethanol and/or saline to optimize the characteristics of the composition through routine experimentation. It would be further within the scope of the artisan to optimize the amounts of compound I, cyclodextrin and ethanol in said composition for the intended use.

The instant claims recite a composition comprising compound I and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 29 Dec 2008, and Applicant's Remarks, filed 29 Apr 2009, have been fully considered and not found to be persuasive.

Applicant notes that Mittendorf does not disclose cyclodextrin, let alone any aqueous formulation comprising the instant Compound (I) and cyclodextrin. Mittendorf teaches the formulations comprising the active compound prepared using solvents, excipients, emulsifiers and/or dispersants, and organic solvents as auxiliary solvents if

water is used as the diluent (column 37, lines 25-30), however Mittendorf does not disclose any formulation comprising cyclodextrin.

Applicant notes that Szabo discloses WIN 55,212-2 and CP 55,940, which have fundamentally different structures from instant Compound (I). Examiner has previously asserted that, with regard to structural equivalence for determining solubility and formation of inclusion complexes with cyclodextrin, structural relationships are based on principles of physical organic chemistry, such as size of the molecule and polarity of the molecule. Applicant notes that one skilled in the art expect the physical organic chemical properties would be dissimilar due to the noted fundamentally different structures. To support Examiner's assertion that one of skill in the art would expect structural equivalence specifically with regard to for determining solubility and formation of inclusion complexes with cyclodextrin evidence of the level of skill in the art is provided by Liu (Water-Insoluble Drug Formulation, 2000, p111-140, cited in PTO-892). Liu teaches the technique of solubility enhancement by applications of cyclodextrin is well known (page 111, paragraph 1). Liu teaches the structural aspects of complexation largely depends on the complexed compound's size compatibility with the dimensions of the CD cavities (page 115, especially paragraph 1). Based on the structures of instant Compound (I), WIN 55,212-2 and CP 55,940 one of skill in the art would reasonably expect them to have a similar size compatibility with the dimensions of a given CD cavity, because to a first approximation instant Compound (I) falls between WIN 55,212-2 and CP 55,940 in size based on the size of the ring moieties.

Applicant notes that the formulation of cannabinoid receptor antagonist SR141716A does not include cyclodextrin. However, it is noted that Szabo teaches 2-hydroxypropyl-β-cyclodextrin as a "solvent" (page 821, left column paragraph 2), where as the cannabinoid receptor antagonist SR141716A is taught in a formulation having an organic solvent in water, 50% ethanol (page 281, paragraph 2 in section Drugs). Rather than teaching away from the formulation taught by Mittendorf including cyclodextrin taught by Szabo, this may be interpreted as teaching the 2-hydroxypropyl-β-cyclodextrin as a "solvent" as an equivalent solubilizer as an organic solvent, such as ethanol in the case of SR141716A, as an auxiliary solvent if water is used as the diluent as taught by Mittendorf (column 37, lines 25-30). This interpretation is consistent with the level of skill in the art regarding solubility enhancement by applications of cyclodextrin as evidenced by Liu.

Applicant notes that obviousness cannot be based upon hindsight reasoning using the instant claims as a "blue print". However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As noted above, Mittendorf teaches the formulations comprising the active compound prepared using solvents, excipients, emulsifiers and/or dispersants, and organic solvents as auxiliary solvents if water is used as the diluent (column 37, lines

25-30). Szabo teaches the 2-hydroxypropyl-β-cyclodextrin as a "solvent" when water is used as the diluent, and may be interpreted as it being equivalent to an organic solvent as an auxiliary solvent such as ethanol. In view of the evidence of the level of skill in the art provided by Liu, the *prima facie* case of obviousness takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made.

Claims 1- 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000).

Mittendorf and Szabo teach as set forth above. The references are silent regarding the pH of the solutions or the use of citric acid.

Nakazi teaches that a citrate buffer (pH 4.8) is a suitable vehicle for cerebral infusion of the cannabinoid agonists, WIN 55,212-2 and CP 55,940. See paragraph bridging pages 20 and 21.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising said compound for infusion using any suitable physiologically solution for administration as taught by Mittendorf. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further

obvious to modify this composition by adjusting it to a suitable pH for cerebral infusion with a citrate buffer with a reasonable expectation of success.

The instant claims recite a composition comprising compound I and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 29 Dec 2008, and Applicant's Remarks, filed 29 Apr 2009, have been fully considered and not found to be persuasive.

Applicant's remarks regarding Mittendorf in view of Szabo are addressed as above.

Claims 1-4 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Yamada (US 5,807,337).

Mittendorf and Szabo teach as set forth above. The references teach the infusion of cannabinoid receptor agonists but are silent regarding the description of the infusion apparatus used in each reference.

It is well known in the art to use an infusion apparatus for the continuous administration of therapeutic agents, and the drug-contacting surfaces are typically plastic. See, for example, Yamada at col 5, lines 15-25.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the recited composition, as set forth above. It would be

further obvious to combine the composition with an infusion apparatus to form a kit for administration of the composition. It would be within the scope of the artisan to select any appropriate apparatus for this utility.

Response to Applicant's Remarks:

Applicant's Remarks, filed 29 Dec 2008, and Applicant's Remarks, filed 29 Apr 2009, have been fully considered and not found to be persuasive.

Applicant's remarks regarding Mittendorf in view of Szabo are addressed as above.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623